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LABETALOL OR NIFEDIPINE AS ANTIHYPERTENSIVE TREATMENT FOR CHRONIC HYPERTENSION IN PREGNANCY: A RANDOMISED CONTROLLED FEASIBILITY TRIAL

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ABSTRACT

Data from randomised controlled trials to guide antihypertensive agent choice for chronic hypertension in pregnancy are limited; this study aimed to compare labetalol and nifedipine, additionally assessing the impact of ethnicity on treatment efficacy. Pregnant women with chronic hypertension (12^{+0}-27^{+6} weeks' gestation) were enrolled at four UK centres (August 2014 to October 2015). Open-label first-line antihypertensive treatment was randomly assigned: labetalol (200-1800 mg/day) or nifedipine modified release (20-80 mg/day). Analysis included 112 women (98%) who completed the study (labetalol n=55, nifedipine n=57). Maximum blood pressure (BP) post-randomisation was 161/101 mm Hg with labetalol versus 163/105 mm Hg with nifedipine (mean difference systolic: 1.2 mm Hg (-4.9 to 7.2 mm Hg), diastolic: 3.3 mm Hg (-0.6 to 7.3 mm Hg)). Mean BP was 134/84 mm Hg with labetalol and 134/85 mm Hg with nifedipine (mean difference systolic: 0.3 mm Hg (-2.8 to 3.4 mm Hg), and diastolic: -1.9 mm Hg (-4.1 to 0.3 mm Hg)). Nifedipine use was associated with a 7.4 mm Hg reduction (-14.4 to -0.4 mm Hg) in central aortic pressure, measured by pulse wave analysis. No difference in treatment effect was observed in Black women (n=63), but a mean 4 mm Hg reduction (-6.6 to -0.8 mm Hg; P=0.015) in brachial diastolic BP was observed with labetalol compared to nifedipine in non-Black women (n=49). Labetalol and nifedipine control mean BP to target in pregnant women with chronic hypertension. This study provides support for a larger definitive trial scrutinising the benefits and side effects of first-line antihypertensive treatment.

Key words: pregnancy complications, hypertension, antihypertensive agents, labetalol, nifedipine

INTRODUCTION

Data to inform prescribing of antihypertensive treatments for chronic hypertension in pregnancy are sparse and subsequently no consensus on the optimal agent(s) exists.[1, 2] The prevalence of chronic hypertension in pregnancy is estimated at 3%,[3] but this figure is set to increase with rising maternal age and the global obesity epidemic.[4, 5] Given that chronic hypertension is associated with significantly increased adverse maternal and perinatal outcomes compared to the general pregnant population,[6] defining optimal antihypertensive treatment(s) is warranted.

A Cochrane review examining trials (including over 4000 women) in mild to moderate hypertension in pregnancy (combining chronic and gestational hypertension) concluded that though the incidence of severe hypertension is reduced with antihypertensive treatment, no reduction in the incidence of adverse maternal and perinatal outcomes has been demonstrated.[7] There have been additional concerns that antihypertensive treatment might increase the risk of fetal growth restriction.[8] However, more recent evidence from the Control of Hypertension In Pregnancy Study concluded that 'tight control' to a diastolic target of 85 mm Hg (compared to 'less-tight control' to a diastolic target of 105 mm Hg) did not increase the risk of pregnancy loss or high-level neonatal care in women with non-severe chronic and gestational hypertension, no proteinuria and a singleton pregnancy.[9] This study also demonstrated that the incidence of severe maternal hypertension was significantly increased with 'less-tight' control, which was associated with an increased risk of serious maternal morbidity in these women (post-hoc analysis).[10] The study highlights the need to determine which antihypertensive agent(s) provides optimal control of chronic hypertension in pregnancy to ameliorate these risks.

Choice of antihypertensive outside pregnancy depends on ethnicity with those of African/Caribbean family origin receiving calcium-channel blockers as first-line agent[11] and is thought to relate to differences in the pathophysiology causing hypertension in those of differing ethnic backgrounds.[12] Ethnic disparity in maternal and perinatal outcome in the general pregnant population is well described and likely to be multifactorial.[13] To our knowledge, no randomised controlled trials have investigated the impact of ethnicity on efficacy of antihypertensive treatment in pregnancy. The aims of the 'Pregnancy And chronic hypertension: NifeDipine versus lAbetalol as antihypertensive treatment' study were three-fold: to assess feasibility of such a randomised controlled trial, to evaluate mechanistic treatment effects, and to examine the impact of ethnicity on efficacy of nifedipine (a calcium-channel blocker with a well-established safety profile in pregnancy) with labetalol (currently recommended as first-line by national UK guidance)..

METHODS

The study was an open-label, phase four, randomised controlled clinical trial (EudraCT Number 2013-003144-23), registered with International Standard Randomised Controlled Trials Number (DOI 10.1186/ISRCTN40973936, www.isrctn.com); the protocol, and other study literature were approved by the UK Research Ethics Committee (REC number 13/EE/0390). Women of varied ethnicities were enrolled by study investigators using written informed consent at four consultant-led National Health Service (NHS) obstetric units in the United Kingdom (Guy's and St Thomas' NHS Foundation Trust, Central Manchester University NHS Foundation Trust, University of Leicester Hospitals NHS Trust and St George's University Hospitals NHS Foundation Trust). The eligibility criteria included:

women with a prenatal diagnosis of chronic hypertension (treated or untreated) or blood pressure (BP) readings ≥140 mm Hg systolic or ≥/90 mm Hg diastolic prior to 20 weeks' gestation requiring antihypertensive treatment prior to 27+6, as defined by the International Society for the Study of Hypertension in Pregnancy,[14] gestation between 12^{+0} and 27^{+6} weeks (to allow for second trimester blood pressure nadir), singleton pregnancies, aged over 18 years, and the ability to provide written informed consent. Women were excluded if they had a contraindication (relative or absolute) to either antihypertensive agent, such as labetalol in women with asthma. Details of the randomisation process, intervention and outcome measures are contained in the Supplemental Material (Supplemental Methods: Randomisation, Intervention and Outcome Measures).

Statistical analysis

For the primary analysis, the intention to treat principle was applied; women were analysed in the groups into which they were randomly allocated regardless of allocation received. The statistical software Stata/SE version 14 for Windows was used for all analyses. The number and percentage were calculated for binary and categorical variables. The mean and standard deviation (SD) or the median and interquartile range (IQR) were calculated for continuous variables. Linear regression with robust standard errors (SE) were used for the primary and other continuous outcomes. Adjustment was made for baseline covariates including, ethnicity (Black (determined by self-report of whether the woman had a parent or grandparent who was African or Caribbean) versus non-Black (all other ethnicities)), gestational age at randomisation, and centre. For continuous measures, an adjustment was also made for corresponding baseline measurement (systolic BP at randomisation for the primary clinical outcome). For binary outcomes, binary regression with a log link was used

to calculate risk ratios (RR). Analysis of the primary clinical outcomes was repeated excluding women delivering their baby before 24 completed weeks of pregnancy, as women who deliver before viability did not complete the intended course of treatment.

Subgroup analyses assessing the impact of ethnicity on treatment efficacy were performed using linear regression adjusting for baseline co-variates. Results are reported for both groups and an interaction test carried out for any moderation of the treatment effect by the subgroup. A sensitivity analysis was also performed to evaluate the impact of date recruited on the primary outcome, using linear regression with a treatment × time interaction. Explanatory analysis of longitudinal urinary protein: creatinine ratio (PCR) (excluding women with chronic kidney disease) and pulse wave measures was conducted using interval regression models on log-transformed data allowing for gestation effects and the baseline measures. Group means and treatment effects were calculated as geometric means and ratios of geometric means given that log transformations were used. Serious adverse events and adverse events were collated and listed by allocation and grouped by symptom. Treatment effects were calculated as estimated differences in the mean or risk ratios with 95% confidence intervals.

RESULTS

Between August 2014 and October 2015, 265 women were screened to enter the trial (Figure 1), of whom 65% met all eligibility criteria. Nine women (3%) were ineligible as they had a concurrent diagnosis of asthma and labetalol was therefore contraindicated. There were no women with a contraindication to nifedipine modified release. Of eligible women, 66% agreed to participate. The most common reason given for declining participation was

reluctance to change from current antihypertensive therapy. Recruitment stopped when the enrolment target was reached as per the pre-specified primary process outcome. 114 women with singleton pregnancies and a diagnosis of chronic hypertension were randomised to first-line antihypertensive therapy with either labetalol (n=56) or nifedipine (n=58). The participants not included in the analysis included one woman lost to follow-up (she emigrated during her pregnancy), and one who withdrew due to time constraints waiting for dispensing from the clinical trials pharmacy (no further information was available).

Most baseline maternal characteristics at enrolment were similar between treatment groups (Table 1), except that time from diagnosis of chronic hypertension to study entry was longer in the labetalol group (54 versus 20 months), and the number of women with renal disease (labetalol n=5 versus nifedipine n=9) and diabetes (labetalol n=5 versus nifedipine n=8) at study entry was higher in the nifedipine group. The results were adjusted allowing for these differences, but this had no significant impact on the outcomes observed (P=0.29).

Feasibility Outcomes

The feasibility of conducting this trial in women with chronic hypertension in pregnancy was confirmed (Table 2), with the enrolment target reached over 14 months. Recruitment rate was 2.6 women per month (range of 1.2-3.7 per month). Disparity in recruitment rate by centre was associated with variation in the incidence of chronic hypertension in pregnancy at each centre. Women self-identifying as of Black ethnicity accounted for 56% of those enrolled, confirming feasibility of recruiting women of differing ethnic backgrounds. Geographical variation in the proportion of Black women enrolled was seen reflecting the

demographics of the local population of each hospital. The assigned intervention was discontinued by 12 women due to side effects of the medication; seven (13%) in the labetalol arm and five (9%) in the nifedipine arm.

Clinical Outcomes

Labetalol and nifedipine demonstrated effectiveness at controlling BP to therapeutic target in women with chronic hypertension in pregnancy (mean BP post-randomisation: labetalol 134/84 mm Hg versus nifedipine 134/85 mm Hg). No difference was observed in highest brachial BP following randomisation to either treatment arm (Table 3). Sensitivity analyses included a per-protocol analysis excluding those who withdrew from their assigned intervention, analysis excluding those who delivered before 24 weeks' gestation, and evaluating the impact of date recruited; there was no impact on the results for any of these analyses. Further analysis of the number of days with brachial BP readings out of target ≥160 mm Hg systolic, ≥150 mm Hg systolic, and <80 mm Hg diastolic demonstrated no difference between treatment groups.

Secondary maternal and perinatal outcomes (Table 4) showed more women receiving nifedipine developed superimposed pre-eclampsia than those allocated labetalol, but these differences were not significant (RR 1.78; 0.84-3.77). The same number of women in each group were diagnosed with early onset superimposed pre-eclampsia prior to 34 weeks' gestation (n=6 (11%) in each treatment group). The number of women requiring additional oral antihypertensive agents was comparable between groups. There was a greater proportion of women treated with intravenous antihypertensive agents in the nifedipine group (14% versus 4%). The proportions of women requiring induction of labour and

caesarean section were comparable. The median gestation at delivery was similar between groups. Adverse maternal outcomes were reported for 6 (11%) women in the labetalol arm compared to 8 (14%) in the nifedipine arm (Supplemental Table S1).

Six women delivered their baby before 24 weeks and three women had a stillbirth after 24 weeks' gestation. Four had late miscarriages (one in the labetalol group and three in the nifedipine group). Two women (one in each treatment group) underwent second trimester termination of pregnancy after enrolling in the study (one for abnormal amniocentesis result post-randomisation and one for severe early onset growth restriction). There were two stillbirths in the labetalol group (both with severe early onset growth restriction) and one in the nifedipine group (trisomy 13 diagnosed on amniocentesis after study enrolment). There was no significant difference in mean birthweight: 2960 g in the labetalol arm versus 2730 g in the nifedipine arm (adjusted mean difference -240 g; -590, 110 g). There was a high proportion of babies born below the 10^{th} and 3^{rd} birthweight centile in each treatment group. Neonatal unit admission was slightly lower in the labetalol group compared to the nifedipine group (22% versus 29%). Adverse neonatal outcomes were reported for 11 (22%) infants in the labetalol arm and 17 (33%) infants in the nifedipine arm (Supplemental Table S2). Maternal and neonatal health resource use was similar between treatment groups (Supplemental Table S3).

A pre-specified exploratory subgroup analysis of the impact of ethnicity on efficacy of each treatment did not show any significant difference in mean systolic or diastolic brachial BP in Black women (systolic 0.5 mm Hg; -4 to 5 mm Hg; diastolic 0.1 mm Hg; -3 to 3 mm Hg). No difference in mean systolic BP was seen between treatment groups in the non-Black women

(-0.4 mm Hg; -4 to 3 mm Hg), but a 4 mm Hg (-6.6 to -0.8 mm Hg; P=0.015) reduction in mean diastolic BP was seen in the labetalol arm in non-Black women.

Mechanistic Outcomes

Pulse wave analysis was performed in a subgroup of 83 women at three centres (nifedipine n=43, labetalol n=40). There was a mean 7.4 mm Hg decrease (-0.4 to -14.4 mm Hg) in central aortic pressure between randomisation and delivery in those assigned nifedipine compared to labetalol; this difference in reduction of central pressure was not observed in the peripheral blood pressures, which were the same between treatment groups. Augmentation index was 8.2% lower (-3.0 to -13.3%) in those assigned nifedipine compared to labetalol, though a sensitivity analysis examining the impact of centre on this finding demonstrated significant variation in this parameter by centre. There was no significant difference in pulse wave velocity between treatment groups (Table 3).

Analysis of gestational change in urinary PCR by treatment group included samples from 73 women (collected at three centres) without chronic kidney disease (nifedipine n=35, labetalol n=38). The PCR increased by 44% (21 to 71%) across gestation post-randomisation in women assigned nifedipine compared to women prescribed labetalol (Supplemental Figure S1). The mean PCR post-randomisation was 11.5 mg/mmol (SD 1.9) in the nifedipine group compared to 7.5 mg/mmol (SD 1.8) in the labetalol group. The analysis was repeated excluding the women who developed superimposed pre-eclampsia (labetalol n=35 versus nifedipine n=27) with minimal effect on the results; PCR increased by 43% (18 to 74%) and the mean PCR post-randomisation was 11.5 mg/mmol (SD 1.9) in the nifedipine group compared to 7.4 mg/mmol (SD 1.9) in the labetalol group.

Adverse Events and Acceptability

There were four Serious Adverse Events reported, all for unplanned hospital admissions not related to the pregnancy; one was in the labetalol arm (admission for epistaxis) and three in the nifedipine arm (one case of gastroenteritis, one case of deep vein thrombosis and one case of influenza). None were deemed to be related to the assigned intervention. The adverse events reported are presented in Supplemental Table S4 and are consistent with the Summary of Product Characteristics as expected side-effect profile for each drug. In the labetalol group, 21 (38%) women reported an adverse event compared to 15 (26%) in the nifedipine group. The postnatal questionnaire was answered by 34% of the women who completed the study. When asked if they would take the same treatment again in another pregnancy, 72% of the women taking labetalol said they 'definitely would' compared to 90% of those assigned nifedipine, and 11% of those assigned labetalol said they 'probably would not' take the treatment again compared to 5% of those assigned nifedipine.

DISCUSSION

To our knowledge this is the first randomised controlled trial comparing labetalol and nifedipine for control of chronic hypertension in pregnancy. The maximum and mean BP post-randomisation were comparable between treatment groups; given the contraindications and potential side effects of these drugs, evidence that they have similar ability to control hypertension to treatment target is beneficial. Evidence from the Control of Hypertension In Pregnancy Study demonstrates maternal benefit of 'tight control' of BP utilising antihypertensive agents in reducing the incidence of severe hypertension without an increase in adverse perinatal outcomes.[9] This is the largest head-to-head trial in pregnant

women with chronic hypertension assessing effectiveness of antihypertensive agents in controlling BP. Randomised controlled trials comparing antihypertensive treatment of chronic hypertension in pregnancy are limited and most were conducted at least 20 years ago; only three previous head-to-head studies (total 101 women) have compared the incidence of severe hypertension between randomised treatment groups (RR 1.1; 0.71-1.81).[1] This study was not powered to assess variation in the secondary maternal and perinatal outcomes, so further larger trials should evaluate differences in the incidence of superimposed pre-eclampsia, preterm delivery and small for gestational age infants. Variation in treatment effect by ethnicity was also noted, with labetalol having a greater effect on reducing diastolic BP in non-Black women, as previously demonstrated with beta-blocker use outside pregnancy.[15] The clinical significance of this potential difference needs to be established.

Recruitment to randomised controlled trials of medication in pregnancy is challenging in view of the real and perceived risk of fetal harm. We confirmed the feasibility of conducting a randomised controlled trial investigating effectiveness of first-line antihypertensive agents for the treatment of chronic hypertension in pregnancy. Of the women meeting all eligibility criteria to enter the study, two-thirds consented to participation and 98% completed the study. Ethnic diversity in recruitment was also achieved, enabling investigation of variation in treatment efficacy. Demonstrating feasibility is important given the costly nature of large multicentre studies and need for suitable pragmatic designs to ensure definitive studies will fully answer the research questions posed.[16]

Nifedipine was associated with reduced central aortic pressure and augmentation index (markers of arterial stiffness). Calcium-channel blockers (versus beta-blockers) have been demonstrated to lower central aortic pressure in the Conduit Artery Functional Endpoint Study (non-pregnant hypertensive population).[17] The exact mechanism behind these haemodynamic differences is not clear, but this finding in combination with the Anglo Scandinavian Cardiac Outcomes Trial results (of which the Conduit Artery Functional Endpoint Study was a subgroup analysis) suggested a greater decrease in long term cardiovascular risk with calcium-channel blockers as first-line antihypertensive agent compared to beta-blockers, perhaps mediated through reduction in central aortic pressure.[18] National guidance no longer recommends beta-blockers as first-line antihypertensive treatment outside pregnancy; calcium-channel blockers are recommended as first-line antihypertensive treatment in Black women and angiotensin converting enzyme inhibitors (avoided in pregnancy due to fetal risks) are recommended for women under 55 years of age of other ethnic backgrounds.[11] African and Caribbean women are at increased risk of chronic hypertension and its associated cardiovascular morbidity, from a younger age than women of other ethnic origins.[19] There is evidence that maternal and perinatal outcomes vary by ethnic background.[13] The implications of first-line treatment recommendations outside pregnancy on the selection of antihypertensive agents in pregnancy needs to be established.

Increased proteinuria across gestation with nifedipine (compared to labetalol) was demonstrated even when those who developed superimposed pre-eclampsia and with pre-existing renal disease were excluded from the analysis. Proteinuria is known to increase across gestation in normotensive pregnancy due to increased glomerular filtration.[20] In this

cohort the mean PCR increased post study enrolment by 2.4 mg/mmol. It is not clear if the difference in proteinuria between treatment groups is a beneficial effect of labetalol or a side effect of nifedipine on renal function, and the clinical significance is unclear given the concentrations fall within the normal range. It seems probable that this is a side effect of nifedipine given similar findings in a Cochrane systematic review of an increase in proteinuria/pre-eclampsia in women with mild to moderate hypertension in pregnancy randomised to calcium-channel blockers versus none (four studies, 725 women; RR 1.40 (1.06-1.86)),[7] however the difference in the incidence of pre-eclampsia between treatment groups within our study was not significant. Studies in non-pregnant individuals with hypertension and chronic kidney disease suggest that dihydropyridine calcium-channel blockers (including nifedipine) are less effective at reducing proteinuria and therefore offer less renal protection than other antihypertensive agents.[21] Investigation into the mechanism behind these differences has suggested that glomerular hypertension may be caused by dihydropyridine calcium-channel blockers that dilate the afferent but not the efferent renal arterioles.[22] The variation in mechanism of action of antihypertensive agents in pregnancy needs to be explored further given that crossing a threshold of proteinuria is utilised in the diagnosis of pre-eclampsia; however the benefits of hypertensive control may outweigh a small increase in proteinuria.

The strengths of this study include enrolment at four UK centres, reducing the risk of clinical practice bias. The study was designed and conducted as a randomised controlled trial in-line with CONSORT guidance.[23] A computer-generated minimisation protocol was used to ensure balance within groups of maternal baseline characteristics. This reduced the risk of imbalance of baseline characteristics within treatment arms affecting the outcomes of the

study. The study enrolled women with primary and secondary hypertension (predominantly due to renal disease), which increases generalisability of the results; however this introduced potential bias as reflected in the imbalance of women with chronic kidney disease and diabetes between treatment groups.

Whilst this study has confirmed feasibility, a larger definitive study is required to assess further the effectiveness of labetalol and nifedipine as antihypertensive treatment in pregnancy complicated by chronic hypertension. The study was not powered to answer the additional question of ethnic variation in effectiveness of first-line antihypertensive agents in pregnancy, but demonstrated the feasibility of recruiting women of many ethnic groups. The study was open-label subjecting the results to potential performance bias.[24] It was considered clinically not feasible to mask allocation to clinicians and women in view of the differing recommended dosing frequency and need to escalate treatment and add a second agent where needed. Criteria for addition of second or third antihypertensive agent were not stipulated in the protocol, as this study aimed to investigate pragmatic clinical effectiveness rather than efficacy. Although methyldopa was considered for inclusion in the comparison, the sites chosen for this feasibility study indicated that methyldopa was not used as a first-line antihypertensive agent in their practice and thus a head-to-head labetalol versus nifedipine comparison was undertaken. Recent evidence (though not from a randomised head-to-head comparison) suggested that this agent may be associated with benefit in maternal and perinatal outcome compared to labetalol, and it should be considered for inclusion in a definitive trial.[25] In the non-pregnant population there is evidence that some antihypertensive agents have additional therapeutic benefits beyond reduction in arterial blood pressure, including anti-inflammatory and oxidative stress

lowering properties.[26] Given the role of inflammation and oxidative stress in the pathophysiology of pre-eclampsia,[27] future research should further explore the mechanistic actions of each drug to establish if other therapeutic benefits exist in pregnancy. In addition, given the variation in dosing regimens and side effect profiles of the first-line antihypertensive agents prescribed in pregnancy, future studies should further assess adherence and acceptability of individual agents.

PERSPECTIVES

Labetalol and nifedipine control mean systolic and diastolic BP to target in pregnant women with chronic hypertension. Good recruitment was demonstrated and mechanistic treatment effects observed. This study provides support for a larger definitive trial scrutinising the benefits and side effects of first-line antihypertensive treatment in pregnancy complicated by chronic hypertension.

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DISCLOSURE OF INTERESTS

Professor Nelson-Piercy reports personal fees from Alliance Pharmaceuticals, UCB Pharmaceuticals, LEO Pharmaceuticals, Sanofi Aventis and Warner Chilcott outside the submitted work. Professor Cruickshank is current President of the Artery Society which has had donations from Servier Pharmaceuticals. The other investigators have no disclosures to report.

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NOVELTY AND SIGNIFICANCE:

1) **What is new?**

- Labetalol and nifedipine are both effective at lowering brachial blood pressure in pregnancy complicated by chronic hypertension.
- Labetalol reduces brachial diastolic blood pressure more than nifedipine in non-Black women.
- Nifedipine reduces central aortic blood pressure significantly more than labetalol in women of varying ethnicities.

2) **What is relevant?**

- Chronic hypertension in pregnancy is associated with adverse maternal and perinatal outcome
- The optimal antihypertensive agent(s) is yet to be identified
- Ethnic variation in antihypertensive treatment effect in women with chronic hypertension in pregnancy is evident and warrants further exploration
- Labetalol and nifedipine demonstrate differing mechanistic treatment effects and the clinical importance of these requires investigation

3) **Summary**

This study provides support for a larger definitive trial scrutinising the benefits and side effects of first-line antihypertensive treatment in pregnant women with chronic hypertension.

FIGURE LEDGENDS:

Figure 1: Flow diagram of trial participants

TABLES:

Table 1: Baseline maternal characteristics at enrolment

Characteristic	**Randomised to labetalol n=56**	**Randomised to nifedipine n=58**
Age at enrolment[*], years	36.0 (32.0-39.1)	35.0 (30.3-38.5)
Gestational age at randomization[*], weeks	16.6 (13.7-21.3)	16.9 (14.6-21.1)
Ethnicity[†]		
Black	30 (54%)	32 (55%)
White	17 (30%)	18 (31%)
Asian	6 (11%)	3 (5%)
Other	3 (5%)	5 (9%)
Current smoker[†]	1 (2%)	1 (2%)
Body mass index[‡], kg/m²	31.2 (7.1)	30.5 (4.9)
Nulliparous women[†]	14 (25%)	13 (22%)
Time since diagnosis of chronic hypertension[*], months	53.5 (8.3-109.5)	20.4 (1.1-75.1)
Type of Chronic Hypertension[†]		
Primary	51 (91%)	48 (83%)
Secondary[§]	5 (9%)	10 (17%)
Diabetes mellitus (type I or type II)[†]	5 (9%)	8 (14%)
Renal disease[†]	5 (9%)	9 (16%)
BP at study entry[*], mm Hg		

Systolic	143 (133-150)	141 (132-151)
Diastolic	92 (85-98)	91 (86-96)
Antihypertensive medication taken at study entry†	41 (73%)	38 (66%)

** median and interquartile range, † number and percentage, ‡ mean and standard deviation, § predominantly due to renal disease*

Table 2: Summary of feasibility outcomes

Feasibility outcome	**Total number enrolled** **n=114**
Women enrolled per centre **number (%)**	
Guy's and St Thomas' NHS Foundation Trust	56 (49%)
Central Manchester University Hospitals NHS Foundation Trust	33 (29%)
University Hospitals of Leicester NHS Trust	12 (11%)
St George's University Hospitals NHS Foundation Trust	13 (11%)
Enrolment rate per centre **(women enrolled per month site recruiting)**	
Guy's and St Thomas' NHS Foundation Trust	3.7
Central Manchester University Hospitals NHS Foundation Trust	2.8
University Hospitals of Leicester NHS Trust	1.2
St George's University Hospitals NHS Foundation Trust	1.9
Mean of all centres	2.6
Proportion of those enrolled of Black ethnicity	
Guy's and St Thomas' NHS Foundation Trust	70%
Central Manchester University Hospitals NHS Foundation Trust	46%
University Hospitals of Leicester NHS Trust	17%
St George's University Hospitals NHS Foundation Trust	77%

Table 3: Effect of treatment on brachial blood pressure and pulse wave analyses

	Randomised to labetalol n=55	**Randomised to nifedipine n=57**	**Adjusted mean difference (95% Confidence Interval)**
Maximum brachial BP, mm Hg			
Systolic	161 (14.7)	163 (19.2)	1.2 (-4.9 to 7.2)
Diastolic	101 (10.2)	105 (11.7)	3.3 (-0.6 to 7.3)
Mean brachial BP, mm Hg			
Systolic	134 (8.5)	134 (9.2)	0.3 (-2.8 to 3.4)
Diastolic	84 (6.6)	85 (5.5)	-1.9 (-4.1 to 0.3)
	n=42	**n=45**	
Central aortic pressure, mm Hg	132 (20.2)	126 (12.9)	-7 (-0.4 to -14.4)
Augmentation index, %	21 (14.9)	13 (11.7)	-8.2 (-3.0 to -13.3)
Pulse wave velocity, m/s	8.8 (1.7)	8.7 (1.5)	-0.1 (-0.4 to 0.7)

Results adjusted for systolic BP at randomisation ethnicity, gestational age at randomisation and centre. Pulse wave analyses were only assessed at three sites, which accounts for the reduction in the number of participants presented.

Table 4: Secondary maternal and perinatal outcomes

	Randomised to labetalol n=55	**Randomised to nifedipine n=57**	**Adjusted difference in mean/median or RR (95% CI)**
Time between randomisation and delivery*, days	134 (39)	127 (44)	
Superimposed pre-eclampsia†	8 (15%)	15 (26%)	1.78 (0.84-3.77)
Superimposed pre-eclampsia <34 weeks†	6 (11%)	6 (11%)	
Additional oral antihypertensive agents†‖			
0	37 (67%)	36 (63%)	
1	15 (27%)	20 (35%)	
≥2	2 (4%)	1 (2%)	
Additional intravenous antihypertensive agents†	2 (4%)	8 (14%)	
Adverse maternal outcome†§	6 (11%)	8 (14%)	
Mode of delivery†			
Spontaneous vaginal delivery	22 (40%)	21 (37%)	
Assisted vaginal delivery	2 (4%)	4 (7%)	
Elective prelabour LSCS	9 (16%)	13 (23%)	
Emergency prelabour LSCS	14 (26%)	11 (19%)	

Emergency LSCS in labour	8 (15%)	8 (14%)	
Estimated blood loss at delivery*, ml	600 (500)	610 (550)	
Gestation at delivery‡, weeks	38.6 (37.7-39.4)	38.0 (36.4-39.1)	-0.6 (-1.3 to 0.1)
Preterm birth <37 weeks†	12 (22%)	20 (35%)	
Preterm birth <34 weeks†	10 (18%)	11 (19%)	
Condition of fetus at delivery†			
Livebirth	51 (93%)	52 (91%)	
Miscarriage	1 (2%)	3 (5%)	
Termination of pregnancy	1 (2%)	1 (2%)	
Stillbirth	2 (4%)	1 (2%)	
Neonatal outcomes	**n=51**	**n=52**	
Birthweight*, g	2957 (790)	2732 (883)	-240 (-589 to 109)
Birthweight <10th centile†	16 (31%)	17 (33%)	
Birthweight <3rd centile†	6 (12%)	10 (19%)	
Admitted to neonatal unit†	11 (22%)	15 (29%)	1.3 (0.7-2.5)
Adverse perinatal outcome†§	11 (22%)	17 (33%)	

**mean and standard deviation, † number and percentage, ‡ median and interquartile range, §details of adverse maternal and perinatal outcomes provided in Supplemental Table S1 and Supplemental Table S2, ‖ of those receiving additional oral antihypertensive agents, 94% (n=16) of the labetalol group were prescribed a calcium-channel blocker and 86% (n=18) of the nifedipine group were prescribed an alpha/beta-blocker. Results adjusted for ethnicity,*

gestational age at randomisation and centre. Risk ratios only calculated for pre-specified secondary outcomes.